RESEARCH PAPER

Impulse control disorder in patients with Parkinson’s disease under dopamine agonist therapy: a multicentre study

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ABSTRACT

Background Impulse control disorders (ICDs) encompass a wide spectrum of abnormal behaviour frequently found in cases of Parkinson’s disease (PD) treated with dopamine agonists (DAs). The main aim of this study was to analyse ICD prevalence with different DAs.

Methods We carried out a multicentre transversal study in younger age and type of DA intake. Oral DA treatment (pramipexole and ropinirole) was associated with higher risk of ICDs compared with transdermal DA (rotigotine): 84/197 (42%) patients treated with oral DA developed ICD, versus 7/36 (19%) patients treated with transdermal DA (Fisher’s exact test <0.01). In univariate analysis, a younger age (p<0.01), treatment with rasagiline (p<0.05), and especially treatment with an oral DA (pramipexole or ropinirole) (p<0.01) were significantly associated with ICD. Multivariate analysis confirmed that oral DA remained significantly associated with ICD (p: 0.014, OR: 3.14; 1.26–7.83).

Conclusions ICD was significantly associated with the use of the non-ergolinic oral DA (pramipexole and ropinirole) when compared with transdermal non-ergolinic DA (rotigotine). Since pramipexole, ropinirole and rotigotine are non-ergolinic DAs with very similar pharmacodynamic profiles, it is likely that other factors including route of administration (transdermal vs oral) explain the difference in risk of ICD development.

Impulse control disorders (ICDs) encompass a wide spectrum of abnormal behaviours including compulsive gambling, compulsive buying and abnormal sexual and eating behaviours.1 ICDs were found to occur frequently in patients with Parkinson’s disease (PD) receiving treatment with dopaminergic medication.1–9 In addition, other compulsive behaviours were also detected in treated PD including compulsive dopaminergic medication usage, punding, compulsive shopping, hobbyism, and aimless wandering5 7 10–17; hence, the broader term ‘impulsive-compulsive disorders’ was also suggested for this medication-related condition.5 18

Dopamine agonists (DAs) have been consistently correlated with ICD,1 3 4–8 14 although younger age, gender, a previous personality profile and the use of other antiparkinsonian medications including levodopa (LD) and monoaminooxidase-B inhibitors are also considered risk factors.2 8–10 19 At present, it is not known whether there is similar risk of ICD with different DAs. A recent survey from Perez-Lloret et al showed that all DAs were related to an increased risk of ICD, thus further supporting a class effect.8

As Weintraub et al pointed out,18 studies intended to analyse ICD in the context of antiparkinsonian medication are particularly difficult for several reasons. First, many patients do not report even serious side effects to their neurologist18; this may be particularly true regarding ICD, either due to embarrassment or because they do not suspect an association with PD treatment.18 Second, several aspects of ICD such as compulsive shopping and extreme hobbyism are not considered abnormal behaviour for many patients; partly for these reasons, ICD are usually under-recognised.18 A further problem arises: with the passage of time, many patients with PD are switched from one medication to another, including different DAs,21 and in some cases a combination of DAs may be used,22 making the link between individual medications (especially individual DA) and ICD difficult to establish.

We carried out a multicentre transversal study to evaluate the presence of ICD in patients with PD chronically treated with a single non-ergolinic DA. The main aim of this study was to analyse ICD prevalence with different DAs (pramipexole, ropinirole and rotigotine).

PATIENTS AND METHODS

We studied patients with PD recruited from Movement Disorders Clinics of five different centres in Spain from July 2012 to April 2013. All patients had PD according to clinical criteria.23 Inclusion criteria were current treatment with a single oral or transdermal DA (pramipexole, ropinirole or rotigotine) for at least 6 months.
Exclusion criteria were previous or concomitant treatment with different DAs (including apomorphine) and dementia.

A transversal assessment was conducted, including demographic and clinical features: Age, gender, duration of disease, duration of DA exposure and concomitant non-DA antiparkinsonian medication (LD, monoaminooxidase-B inhibitor), presence of fluctuations, total Unified Parkinson’s disease Rating Scale (UPDRS) and motor subscale (UPDRS-III) on medication (if fluctuation were present) after their morning dose of medication. Total LD equivalent daily dose was calculated according to previously suggested conversion formulæ. All patients were assessed using self-administered long version of the Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease (QUIP) according to previously recommended optimal cut-off points for maximum sensitivity and specificity. Patients with scores in the range of ICD were classified as ICD+; in addition, ICD subtypes and scores were registered.

Univariate analysis was performed to compare baseline clinical features and presence of ICD among the three DA subgroups (pramipexole, ropinirole and rotigotine), as well as between oral DA (pramipexole or ropinirole) and transdermal DA (rotigotine) subgroups. A multivariate logistic regression analysis of the variables reaching or approaching statistical significance in univariate analysis was designed to rule out for potential confounders.

Statistical study methods included descriptive statistics, Kruskal-Wallis test and Fisher’s test when appropriate, as well as multivariate logistic regression analysis (G-Stat statistical program). Level of significance was set at p<0.05.

The study received approval from the local ethics committees.

RESULTS

Two hundred and thirty-three patients were included in the study (mean age 66±9.7 years). Relevant clinical features of the study population are detailed in table 1. All patients were treated with DA (mean exposure: 5.9 years±4.1 years). One hundred and ninety-seven patients were taking an oral DA including pramipexole (116) and ropinirole (81) while 36 were treated with transdermal rotigotine. Most patients (81.2%) were taking extended release forms of pramipexole and ropinirole (pramipexole retard or requip prolib), although 57.9% were initially treated with immediate release forms of oral DA and over time, switched to an extended release form of the same DA. Table 2 displays clinical variables regarding DA subtypes (pramipexole, ropinirole or rotigotine). Patients taking an oral DA had significantly higher total UPDRS and UPDRS-III scores and had significantly longer exposure time than patients treated with transdermal rotigotine (p<0.05), while total LD equivalent daily dose was higher in the latter group (p<0.01).

Ninety-one patients (39.1%) had ICD as detected by QUIP-scale, but only 28 (12%) spontaneously referred ICD symptoms in clinical interview. Clinical features of ICD are detailed in table 3 and figure 1. Table 4 shows the association between ICD and clinical variables. In univariate analysis, a younger age (p<0.01), treatment with rasagiline (p<0.05) and especially treatment with an oral DA (pramipexole or ropinirole) (p<0.01) were significantly associated with ICD (table 3). There was no significant difference in ICD for those patients treated with immediate release forms of oral DA compared with those treated with extended release forms (Fisher’s test p>0.05). No centre effect was observed either.

In multivariate analysis, treatment with an oral DA remained significantly associated with ICD (p: 0.014) with an OR of 3.14 (95% CI 1.26 to 7.83). Rasagiline (p=0.032, OR 2.12, 95% CI 1.26 to 7.83). There was no significant difference in ICD for those patients treated with immediate release forms of oral DA compared with those treated with extended release forms (Fisher’s test p>0.05).

DISCUSSION

Frequency of ICD is increased in patients with PD since PD itself does not seem to carry an increased risk for development

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Clinical features of patients treated with oral DA and transdermal DA</th>
</tr>
</thead>
<tbody>
<tr>
<td>DA-LEDD (mg)</td>
<td>188.3±81.3</td>
</tr>
<tr>
<td>LD-LEDD (mg)</td>
<td>554.5±227.9</td>
</tr>
<tr>
<td>MAOI</td>
<td>0.2943 (NS)</td>
</tr>
<tr>
<td>Rasagiline</td>
<td>69 (59.5)</td>
</tr>
<tr>
<td>Selegiline</td>
<td>5 (4.3)</td>
</tr>
<tr>
<td>Amantadine</td>
<td>4 (3.5)</td>
</tr>
<tr>
<td>Total LEDD</td>
<td>668.4±372.8</td>
</tr>
<tr>
<td>Scale-ICD</td>
<td>50 (43.1)</td>
</tr>
</tbody>
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Data are shown as number and percentage for qualitative variables and mean±SD for quantitative variables.

Table 1 | Clinical features of the study population |
<table>
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<tbody>
<tr>
<td>n: 233</td>
<td>Gender: male 145 (62.2%); female 88 (37.7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age: 66±9.7 years</td>
<td>UPDRS (TOTAL): 29.9±13</td>
<td></td>
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<tr>
<td>UPDRS III: 20.2±9.18</td>
<td>Exposure time: 5.9±4.1 years</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Motor fluctuations: 96 (41.2%)</td>
<td>DA type:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral 197 (84.5%)</td>
<td>Pramipexole: 116 (49.8%)</td>
<td></td>
<td></td>
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<tr>
<td>Ropinirole: 81 (34.8%)</td>
<td>Transdermal</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Rotigotine: 36 (15.5%)</td>
<td>DA-LEDD: 202±93.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAOI: 154 (66.1%); Rasagiline 148 (63.5%); Selegiline: 6 (2.6%)</td>
<td>Amantadine: 15 (6.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levodopa: 175 (75.1%); LD-LEDD: 600±317.5</td>
<td>Total LEDD: 723.3±422.2</td>
<td></td>
<td></td>
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</tbody>
</table>

Data are shown as number and percentage for qualitative variables and mean±SD for quantitative variables.
of ICD, it is clear that medication plays a main role, and DA intake is consistently reported as a major risk factor. At present, ICD is generally considered a DA class effect and not specific for any DA, however most DA-related behavioural problems were observed with oral DA (including pramipexole or ropinirole) and rarely with transdermal DA (rotigotine).

The main goal of this study was to assess the presence of ICD in patients with PD treated with DA. All the patients included in this study had been taking a single DA for at least 6 months and we excluded patients who had been taking two different DAs at the same time, either in combination or consecutively; for the sake of making the potential relationship between ICD and individual DA clearer.

The frequency of ICD in this particular population was very high: 39% of patients fulfilled the criteria for ICD according to the QUIP questionnaire. This test has been previously validated, with a sensitivity of 100% for patient-completed and informant-completed instruments, although other tests for ICD detection have been proposed. Despite this high prevalence of ICD in patients treated with DA, most patients (and caregivers) did not consider their ICD a serious problem, and only 28/91 patients complained or spontaneously commented on this type of side effect. In this regard, the majority of ICD patients (63/91) might experience what Papay de defined as subsyndromal ICD symptoms. In any case, it is well known that patients with PD are reluctant to report side effects and most medication-related side effects are under-reported.

The group of patients with ICD symptoms (ICD+) differed from those without ICD symptoms (ICD−) in several aspects, including younger age, rasagiline use and especially type of DA intake. Treatment with an oral DA (pramipexole and ropinirole) was strongly associated with a higher risk of ICD compared with transdermal DA (rotigotine), with an OR of 3.14. Forty-two per cent of patients treated with oral DA developed ICD versus 19% taking transdermal DA; this difference appears to be clear enough despite the relatively small number of patients taking rotigotine. Certainly, the number of patients treated with oral DA (pramipexole: 116; ropinirole: 81) was much higher than those treated with transdermal DA (rotigotine: 36 patients). This difference may be explained by the fact that rotigotine was more recently introduced than the other DA; which also explains the longer exposure time in the group of patients treated with pramipexole and ropinirole compared with those treated with rotigotine (see table).

We also studied whether the treatment with a standard or extended release form of oral DA (ropinirole or pramipexole) could be a significant factor for the presence of ICD; we did not find significant differences between standard versus extended release oral DA.

Pramipexole, ropinirole and rotigotine are non-ergolinic DAs with a similar pharmacodynamic profile. The binding profile of pramipexole and ropinirole is rather similar: they mainly interact with dopamine receptors D2, D3 and D4. However, rotigotine also interacts with D2, D3 and D4, as well as with D1 and D5 receptors. The significance of these differences is not well understood, and it would be speculative to use them to explain the differences in our study. Other factors that may explain the different risk of ICD could be the more constant plasmatic levels on rotigotine or perhaps the route of administration (transdermal vs oral route). Transdermal delivery bypasses erratic gastric emptying and may avoid other changes in gastrointestinal motility associated with PD with an impact on plasmatic levels of the drug. This greater stability of plasma levels might explain, at least in part, the relatively low risk of ICD associated with transdermal rotigotine we observed.

<table>
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<th>Table 3 ICDs clinical features</th>
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<tr>
<td><strong>Clinical subtypes</strong></td>
</tr>
<tr>
<td>Hobbyism: 45</td>
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<td>Punding: 29</td>
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<tr>
<td>Hypersusality: 28</td>
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<tr>
<td>Buying: 16</td>
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<tr>
<td>Gambling: 9</td>
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<tr>
<td>Compulsive medication use: 7</td>
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<tr>
<td>Eating disorder: 6</td>
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<td>Walkabout: 3</td>
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<table>
<thead>
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<th>Number of ICDs</th>
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<tr>
<td>Single: 54 (59.3%)</td>
</tr>
<tr>
<td>Multiple: 37 (40.7%)</td>
</tr>
<tr>
<td>Two: 25</td>
</tr>
<tr>
<td>Three: 9</td>
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<tr>
<td>Four: 3</td>
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<table>
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<tr>
<th>QUIP scores</th>
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<tr>
<td>3.2±2.4 (range 1–12)</td>
</tr>
<tr>
<td>Pramipexole 3.2±2.4</td>
</tr>
<tr>
<td>Ropinirole 3.3±2.6</td>
</tr>
<tr>
<td>Rotigotine 3±2</td>
</tr>
</tbody>
</table>

Data are shown as number and percentage for qualitative variables and mean±SD for quantitative variables.

ICD, impulse control disorder; QUIP, Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease.
Finally, we observed an association between ICD and concomitant treatment with rasagiline, with an OR of 2.2. Rasagiline treatment had been previously suggested to be a risk factor for ICD in previous works, although our sample differs from other studies in that our patients were taking DA. This observation might indicate that rasagiline may potentiate the already high risk of developing ICD in patients taking DA, although further studies are warranted to confirm this impression.

We must acknowledge some limitations to our study. First, the number of patients treated with rotigotine is smaller and the exposure time shorter than the oral DA groups. Second, a switch from immediate release to prolonged release formulations of oral DAs was permitted in the inclusion criteria. We cannot thus analyse the generalisation of our results, and prospective studies are warranted to confirm the risk of developing ICD on rotigotine treatment is lower than that of oral DAs as our study suggests.

CONCLUSION

In summary, chronic oral DA (ropinirole and pramipexole) treatment appeared to be associated with a higher risk of developing ICD (detected by QUIP) compared with transcutaneous DA (rotigotine) treatment in our cohort. Rasagiline might have potentiated this increased risk. Further prospective studies are warranted to confirm these findings. Patients with PD on treatment with DA, especially the oral formulations, require a close follow-up for an early detection and management of this potentially serious adverse event.

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Acknowledgements The authors thank Mr Oliver Shaw for his advice on aspects of English language style.

Contributors PJG-R, JCMC and AA-C contributed to conception, design, acquisition of data, analysis and interpretation of data, and wrote the first draft version. AHV, LV, MM, PSA and NOG contributed to acquisition of data. IMF analysed the data. All authors critically revised the manuscript and approved the final version.

Competing interests PJG-R has received research support from Allergan, UCB, Boehringer-Ingelheim, and speaking honoraria from Italfarmaco, UCB, GSK, Allergan, Novartis and Merz. JCMC has received research support from Allergan, Novartis and Abbott, and speaking honoraria from Abbott, Italfarmaco, UCB, GSK, Boehringer-Ingelheim, Allergan, Ipsen, Novartis and Merz.

Patient consent Obtained.

Ethics approval Local ethics committee of each hospital.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES


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*J Neurol Neurosurg Psychiatry* 2014 85: 840-844 originally published online January 16, 2014
doi: 10.1136/jnnp-2013-306787

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